COMPARATIVE STUDY OF EFFICACY OF METHOTREXATE AND MIFEPRISTONE WITH METHOTREXATE IN MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY

Dissertation Submitted to the

THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY
CHENNAI

In partial fulfillment
Of the requirement for the degree of

M.S OBSTETRICS AND GYNECOLOGY
BRANCH II

MADRAS MEDICAL COLLEGE
CHENNAI TAMILNADU

APRIL 2016

CERTIFICATE

This is to certify that this dissertation entitled **"COMPARATIVE STUDY OF EFFICACY OF METHOTREXATE AND MIFEPRISTONE WITH METHOTREXATE IN MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY"** has been done by Dr.V.C.Niveditha, Post Graduate in M.S (Obstetrics and Gynaecology)under my overall supervision and guidance at Govt. Hospital for Women and Child Health, Institute of Obstetrics and Gynaecology, Madras Medical College, Chennai in partial fulfillment of regulations of TamilNadu Dr.M.G.R. Medical University for the award of M.S. Degree in Obstetrics and Gynecology.

Prof. Dr. S. Shoba MD; DGO,
Professor of Obstetrics and Gynaecology
Institute of Obstetrics and Gynaecology,
Madras Medical College,
Chennai.

Prof. Dr. Baby Vasumathi, MD.,DGO.,
Director,
Institute of Obstetrics and Gynecology,
Madras Medical College,
Chennai

Prof. Dr. R. Vimala, MD.,
Dean,
Madras Medical College,
Chennai

DECLARATION

I, Dr. V.C.Niveditha solemnly declare that the dissertation tiltled**"COMPARATIVE STUDY OF EFFICACY OF METHOTREXATE AND MIFEPRISTONE WITH METHOTREXATE IN MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other person for any award, degree or diploma to any other university board either in India or abroad.

This is submitted to The Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.S degree Branch II Obstetrics and Gynaecology to be held in April 2016.

PLACE: **Dr. V.C.Niveditha**

DATE

ACKNOWLEDGEMENT

I am very thankful to **Prof. Dr. R. Vimala, MD.,** Dean, Madras Medical College for her kind permission to carry out this study at Institute of Obstetrics and Gynaecology, Chennai.

I express my sincere gratitude and thanks to **Prof.Dr.Baby Vasumathi, MD.,DGO.,** Director, Institute of Obstetrics and Gynecology, Chennai for her guidance.

I sincerely extend my thanks to **Prof. Dr. S. Shoba MD.,DGO** Professor of Obstetrics and Gynaecology for her encouragement and guidance in conducting the study.

I am very grateful to all **Assistant Professor** at Institute of Obstetrics and Gynaecology, Chennai for their valuable guidance and suggestions in the executing this study.

My sincere thanks to the fellow postgraduates for their help during the course of this study.

Lastly and most importantly, I am indebted to all my patients who willingly participated in this study.

CONTENTS

INTRODUCTION

Now a days ectopic pregnancy is on a raising trend. Increase in number of patients with infertility going for assisted reproductive techniques and increasing sterilization procedure and tubal Re anastomosis procedures has contributed to this rise. With advent of transvaginal ultrasound and beta hCG measurement early diagnosis ectopic pregnancy is possible.

DEFINITION

An ectopic pregnancy is defined as the implantation of the blastocyst anywhere outside the endometrial lining of the uterine cavity. The term ECCYESIS also means ectopic pregnancy. In present world lives are saved by early surgical or medical intervention . In the past women suffered from hemorrhage due to ruptured ectopic pregnancy were managed just by observation or subjected to procedures that has no chance of cure and in some instances may have actually hastened their demise.

OVERVIEW OF LITERATURE

HISTORY OF ECTOPIC PREGNANCY

- Albucasis , an Islamic surgeon first reported ectopic pregnancy in 963 A.D.[1]
- Cordaeus and Polinus proposed a lithopedion that remained in vivo for nearly 28 years.
- Horstius ln the year 1563 found remanants in a abdomen of a women at her third pregnancy.
- In the year 1693 autopsy done on a prostitute revealed a viable unruptured ectopic pregnancy.
- ln the year 1700 Abraham reported abdominal delivery of a dead full term child in a living women .Remarkably the women survived and gave birth to three or more children.
- In 1883 robert Lawson tait performed laparotomy on a ruptured ectopic female and she survived.

- In 1940 with the readily accessible blood products , the significant haemorrhage associated with ectopic pregnancy became less lethal.
- In the year 1966 , immunologic serum tests for human chorionic gonadotropin were developed.[2]
- In 1970, Early gestation sac was first identified using ultrasound.[3]
- In the year 1980 ectopic pregnancy was treated for the first time with methotrexate a folic acid antagonist. Before this methotrexate was used in the treatment of gestational trophoblastic neoplasia. Methotrexate acts on the rapidly dividing cells of gestational trophoblastic neoplasia and inhibits their growth. Methotrexate was successful for treatment of unruptured ectopic pregnancy in early 1990.
- The success of mifepristone for disruption of IUP has been proven. Its success in this regard has led to the consideration of mifepristone as an adjuctive therapy with MTX. Early reports showed that persistent EP was reduced with this combination. [4]

Although the combination seems safe, more recent reports have not confirmed this benefit. Therefore, the combination therapy is still under trial level.

EPIDEMIOLOGY

INCIDENCE

World wide incidence is 1-2 %.[5]

In INDIA it is around 0.3 to 0.7 %.

SEASONAL VARIATION

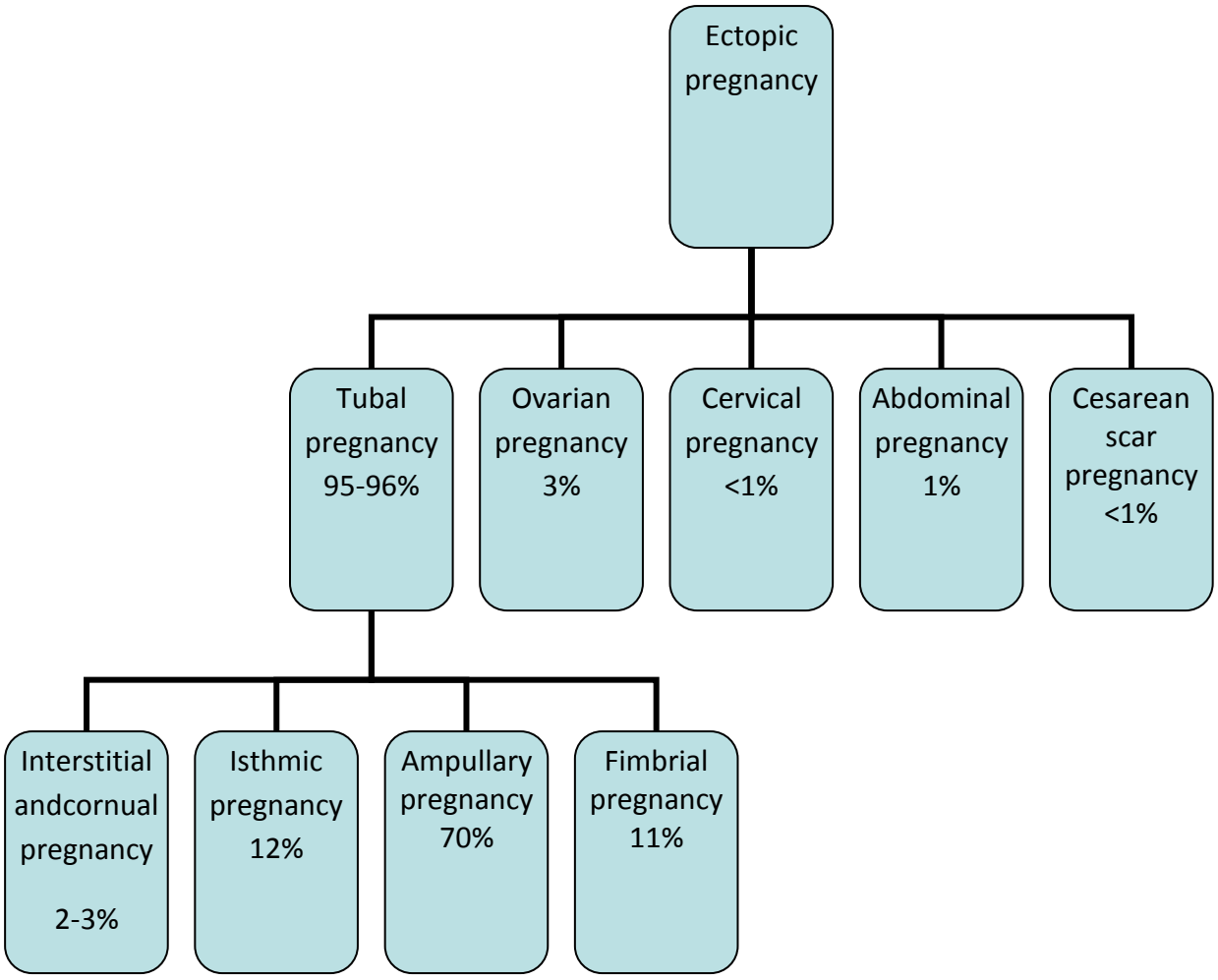
Ectopic Pregnancy Occurs Most Commonly In The Month Of June And December. The reason might be due to photo period and temperature and it may vary with different latitude. Hence ectopic pregnancy may show different seasonal rhythmicities depending on the location of the investigation.[6]

Now a days early daignosis is mainly due to

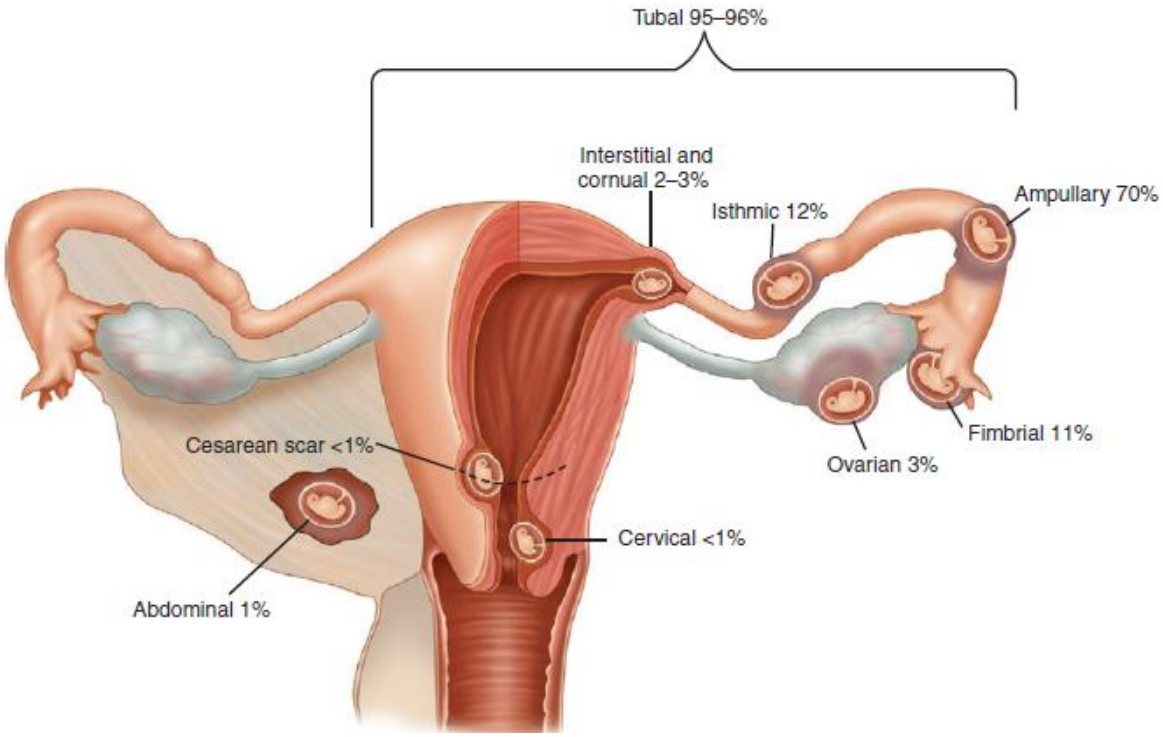
- Beta hCG

- Trans Vaginal Ultrasound

CLASSIFICATION



CLASSIFICATION



RISK FACTORS

- Prior ectopic pregnancy.
- Prior tubal surgery.
- Smoking >20 cigarettes per day.
- Prior STD with confirmed PID by laparoscopy and/or positive test for Chlamydia trachomatis.[7]

- Three or more prior spontaneous miscarriages.
- Age >40 years.
- Prior medical or surgical abortion.
- Infertility >1 year.
- Lifelong sexual partners more than 5.
- Previous IUD use.

SEQUALAE OF ECTOPIC PREGNANCY

MORTALITY

- Most common cause of early death in female is ectopic pregnancy.
- Case fatality rate has decreased ten folds in last 35 years due to current diagnostic and treatment protocols[8].

TUBAL RUPTURE

- Mortality is mainly due to severe hemorrhage from tubal rupture.
- The rupture rate with ectopic pregnancy is 20% to 35%.[9]

- Risk factors for tubal rupture:
    - Having Ovulation induction.
    - Serum beta hCG level exceeding 10,000 IU/L when ectopic pregnancy is first suspected.
    - History of never used contraception.

There may be a difference between an “acute” and a “chronic” ectopic pregnancy in regard to risk of tubal rupture.

ACUTE ECTOPIC PREGNANCIES

- High serum Beta hCG level at presentation.
- Rapid growth leading to an immediate diagnosis.
- Tubal rupture risk rate is high.
- Do not result in early bleeding due to healthy growing trophoblasts.

CHRONIC ECTOPIC PREGNANCIES

- Demonstrate static growth.
- Negative serum Beta hCG.
- Minor repeated ruptures or tubal abortion incites an inflammatory response that leads to formation of a pelvic mass.

TIMING OF TUBAL RUPTURE

- Earlier rupture -if implantation is in the isthmic or ampullary portion of the fallopian tube.
- Later rupture -if the ovum implants within the interstitial portion.

TUBAL DAMAGE

- Initial serum BetahCG level > 5000 IU/L carried a 12-fold increased risk of subsequent tubal obstruction.
- Multidose methotrexate was linked to a higher potential for tubal damage through unclear mechanisms.

PATHOPHYSIOLOGY

HISTOPATHOLOGY

Lack of a submucosal layer within the fallopian tube provides easy access for the fertilized ovum to burrow through the epithelium and allow implantation within the muscular wall. Moreover, absent resistance allows early trophoblast penetration. As the rapidly proliferating trophoblasts erode the subjacent muscularis layer, maternal blood pours into the spaces within the trophoblastic or the adjacent tissue[10]. The anatomic location of a tubal pregnancy may predict the extent of damage.

INFLAMMATION

Acute inflammation has been implicated in the role of tubal damage that predisposes to ectopic pregnancies. Chronic salpingitis and salpingitis isthmica nodosa also have important roles in ectopic pregnancy development. Recurrent chlamydial infection causes intraluminal inflammation and subsequent fibrin deposition with tubal scarring . Oviduct interstitial cells of Cajal are

specialized pacemaker cells responsible for oviduct motility and egg transport. Infections in mice by Chlamydia muridarum, which is similar to human Chlamydia trachomatis, lead to absent spontaneous pacemaker activity and may offer another explanation for how Chlamydia increases ectopic pregnancies in humans.

Another factor involved with oviductal transport of embryos is the cannabinoid receptor (CB1), which is mediated by endocannabinoid signaling. Chronic exposure to nicotine can affect endocannabinoid levels and lead to fallopian tube dysfunction.

A relationship between E-cadherin, an adhesion molecule, and tubal ectopic pregnancy implantation sites was established. Th ey found E-cadherin strongly localized to the tubal embryo implantation site only in women who underwent IVF. This suggests a biologic rather than mechanical factor accounting for the ectopic pregnancies associated with IVF.

CLINICAL PRESENTATION

SYMPTOMS

Classic clinical triad of ectopic pregnancy

- Abdominal pain (98.6%)
- Amenorrhea (74.1%)
- Vaginal bleeding (56.4%)

--50 percent of the patients presents with all the three symptoms.

Patients can also present with other symptoms which is common to early pregnancy

- Sensation of vomiting
- Breast fullness
- Fatigue
- Dizziness

- weakness
- flu like symptoms
- vomiting

--20 percent of the patients with ectopic pregnancy are hemodynamically compromised at initial presentation which is highly suggestive of rupture.[11] Fortunately using modern diagnostic techniques most ectopic pregnancies may be diagnosed before rupture.

SIGN

Some physical finding that have been found to be predictive of ectopic pregnancy include

- Presence of peritoneal signs
- Cervical motion tenderness and Unilateral or bilateral abdominal or pelvic tenderness usually worse on the affected side.

INDICATION FOR EMERGENCY LAPROTOMY

- Guarding and Rigidity.
- Tenderness which is severe.
- Tachycardia.
- Evidence of hypovolemic shock.
- Orthostatic hypotension.

ON EXAMINATION

- The uterus will be slightly soft and enlarged.
- Uterine or cervical motion tenderness.
- Adenexal mass can be palpated. The ectopic pregnancy stimulates endometrial lining which is shed into the vagina and may be seen on a per vaginal examination.

DIAGNOSIS OF ECTOPIC PREGNANCY:

SERUM BETA hCG:

Doubling of Beta hCG is seen in normal pregnancy every two to three days till a level of 10,000-20,000Miu/ml is reached but in ectopic pregnancy the Beta hCG rises at a lesser rate than normal[12]. Hence serial measurements of Beta hCG will help to differentiate between normal from abnormal pregnancies and will also help in monitoring the resolution of ectopic pregnancy after treatment has been started.[13]

The level of Serum Beta hCG above which an ultrasound can visualize a gestation sac inside the uterus in a normal pregnancy is defined as the discriminatory zone of Beta hCG.

- A transvaginal ultrasonography can detect a gestation sac at serum Beta hCG levels of 1500- 1800 mIU/ml. For multiple pregnancy it can diagnose at a level of about 2300 mIU/ml[14].

- An abdomen ultrasound can diagnose a gestation sac at serum Beta hCG levels of 6000-6500 mIU/mL.
    - When an intrauterine pregnancy is absent for Beta hCG levels above discriminatory zone then one should suspect the presence of a ectopic pregnancy or an abortion.

ULTRASONOGRAPHY

Ultrasonography is the most important tool for the diagnosis of ectopic pregnancy[15]. Ectopic pregnancy can reasonably be excluded in cases where an intra uterine sac is visualized with or without cardiac activity. Intrauterine pregnancy can be diagnosed as early as 24 days following ovulation or 38 days following LMP by a Trans vaginal or an Endo vaginal ultrasound which is about one week earlier than trans abdominal ultrasound[16].

When an intrauterine gestation sac is not visualized at Serum Beta hCG levels greater than the discriminatory zone then one should consider the diagnosis of the ectopic pregnancy until proved otherwise[18]. Color-flow Doppler

ultrasonography helps in better diagnosis of ectopic pregnancy by increasing the sensitivity and specificity[17].

USG CRITERIA OF THE VARIOUS TYPES OF EP

TUBAL ECTOPIC PREGNANCY:

lnhomogeneous adnexal mass with empty gestational sac in extrauterine region, and Extrauterine gestational sac containing a yolk and or fetal pole with or without cardiac activity[19].

FIGURE1: TRANSVAGINAL USG OF TUBAL PREGNANCY SHOWING . INHOMOGENEOUS MASS.

FIGURE 2 : TRANS VAGINAL SCAN OF TUBAL ECTOPIC PREGNANCY SHOWING GESTATIONAL SAC WITH FETAL POLE

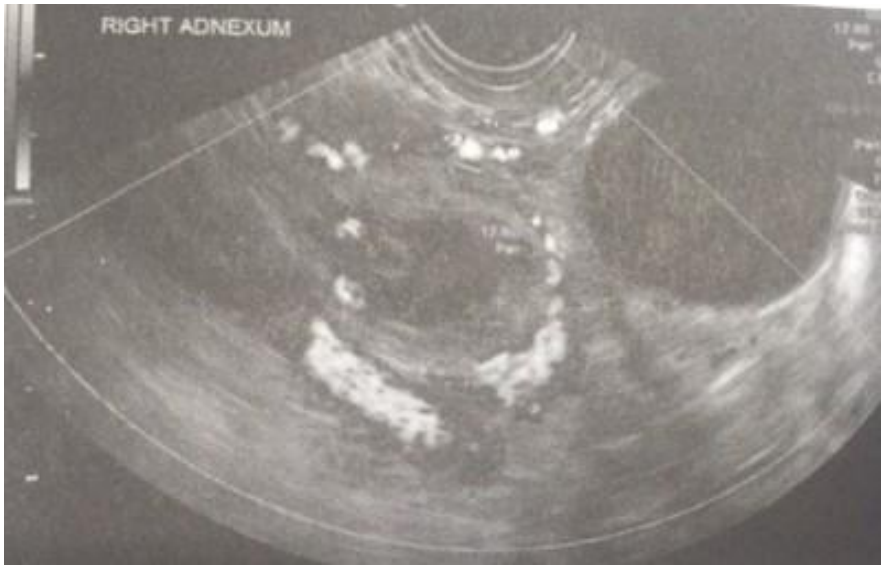


FIGURE 3 EMPTY GESTATIONAL SAC IN FALLOPIAN TUBE (BAGEL SIGN)

FIGURE 4 GESTATIONAL SAC WITH EMBRYONIC POLE AND POSITIVE CARDIAC ACTIVITY

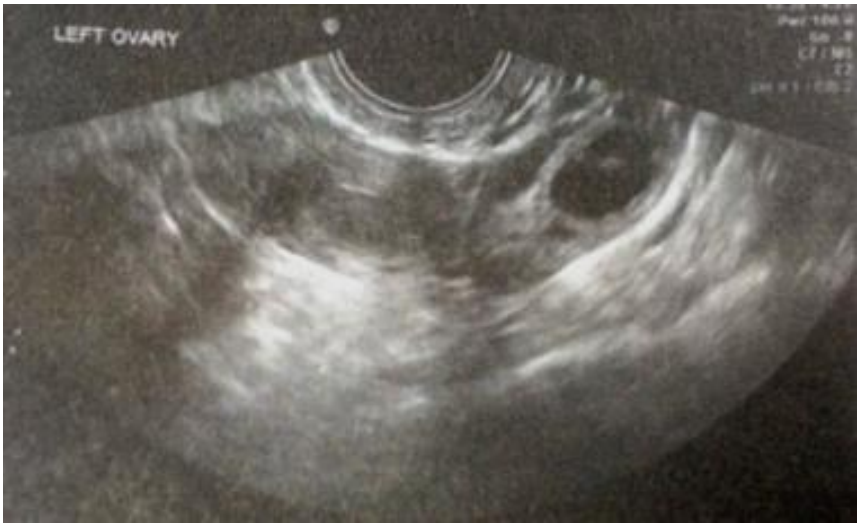


FIGURE 5 INHOMOGENOUS MASS IN THE FALLOPIAN TUBE OR " BLOB SIGN"

INTERSTITIAL ECTOPIC PREGNANCY:

Gestational sac or trophoblastic mass located outside of the endometrial cavity, in the interstitial area, surrounded by a continuous rim of myometrium and Positive interstitial line sign[20].

FIGURE 6 INTERSTITIAL PREGNANCY WITH EMBRYONIC POLE

FIGURE 7 TRANSVAGINAL SCAN IMAGE OF AN INTERSTITIAL ECTOPIC PREGNANCY

CORNUAL ECTOPIC PREGNANCY:

Single interstitial fallopian tube, The gestational sac or trophoblastic mass will be separate from the uterus but completely surrounded by myometrium, and Vascular pedicle adjoining the gestational sac with the unicornuate uterus.

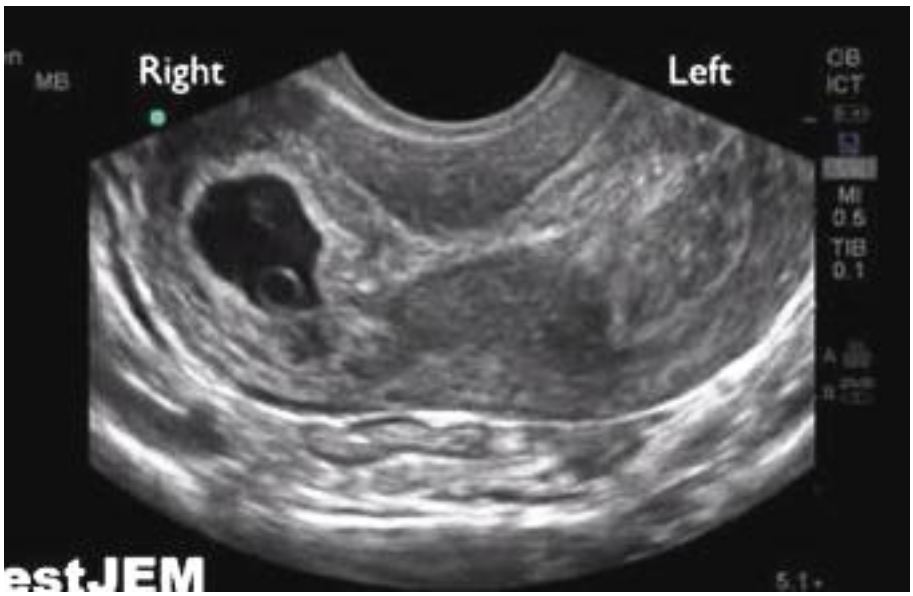


FIGURE 8 CORNUAL ECTOPIC PREGNANCY IN BICORNUATE UTERUS

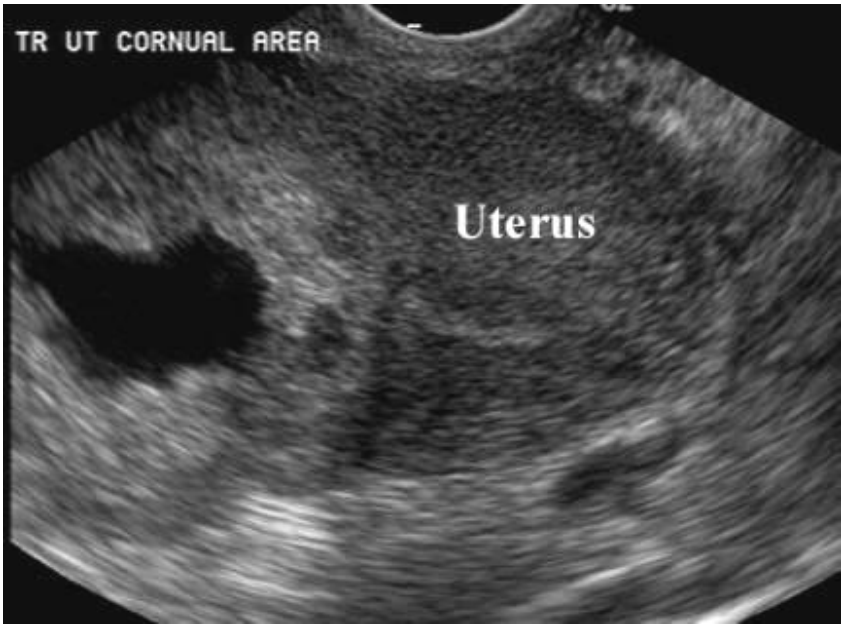


FIGURE 9 CORNUAL ECTOPIC PREGNANCY IN UNICORNUATE UTERUS

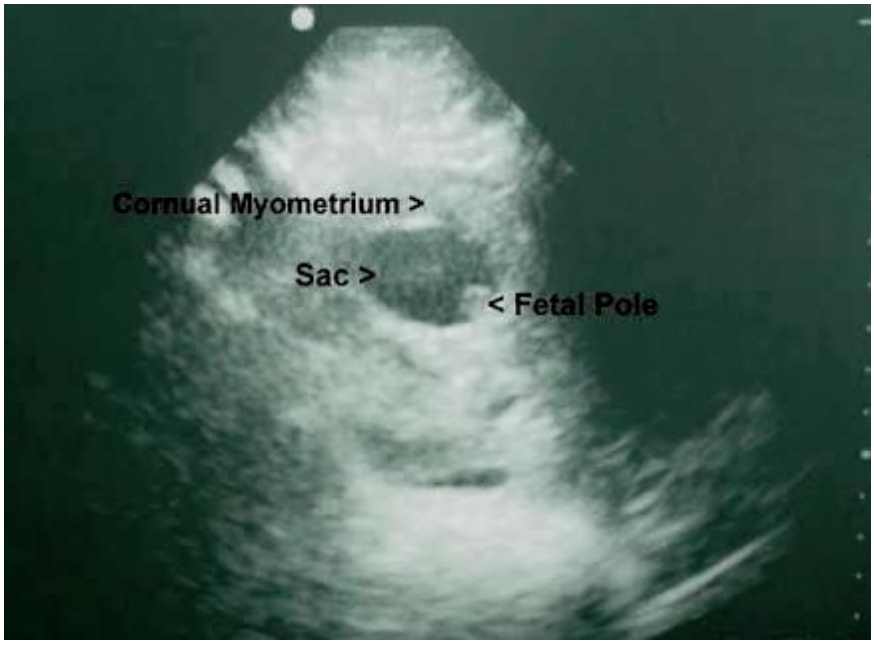


FIGURE 10 CORNUAL ECTOPIC PREGNANCY

CERVICAL ECTOPIC PREGNANCY:

The gestational sac or trophoblastic mass will be present below the level of the internal cervical os, Negative “sliding organ sign”, and Peritrophoblastic circulation on color Doppler examination[21].

FIGURE 11 CERVICAL PREGNANCY. THE GESTATIONAL SAC IS LOCATED BELOW THE LEVEL OF THE CERVICAL INTERNAL OS. ABSENCE OF THE “SLIDING SIGN “ CLINCHES THE ULTRASOUND DIAGNOSIS

CAESAREAN SECTION SCAR ECTOPIC PREGNANCY:

Gestational sac or placental tissue located anteriorly at the level of the internal os covering the visible or presumed site of the previous lower segment caesarean section scar[22,23].

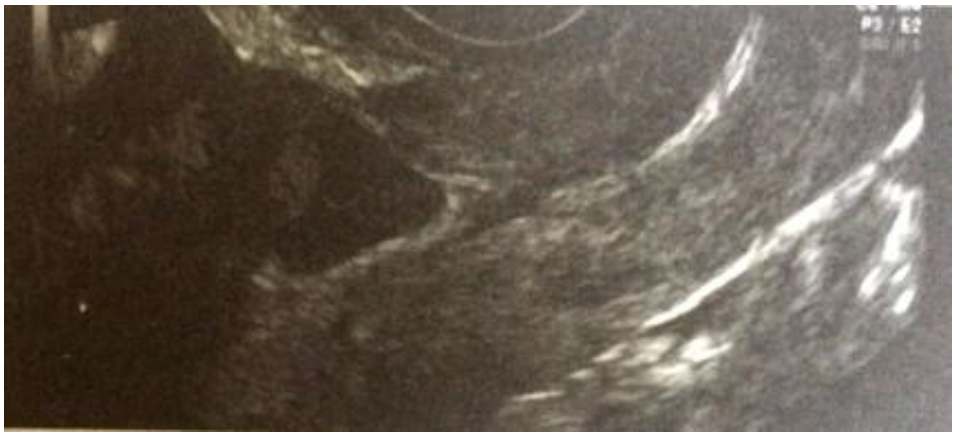


FIGURE 12 CAESAREAN SECTION SCAR ECTOPIC PREGNANCY

FIGURE 13 TRANSVAGINAL SCAN IMAGE OF A CAESAREAN SECTION SCAR PREGNANCY

OVARIAN ECTOPIC PREGNANCY:

Cystic structure with a wide echogenic ring on or within the ovary and negative sliding organ sign[24]

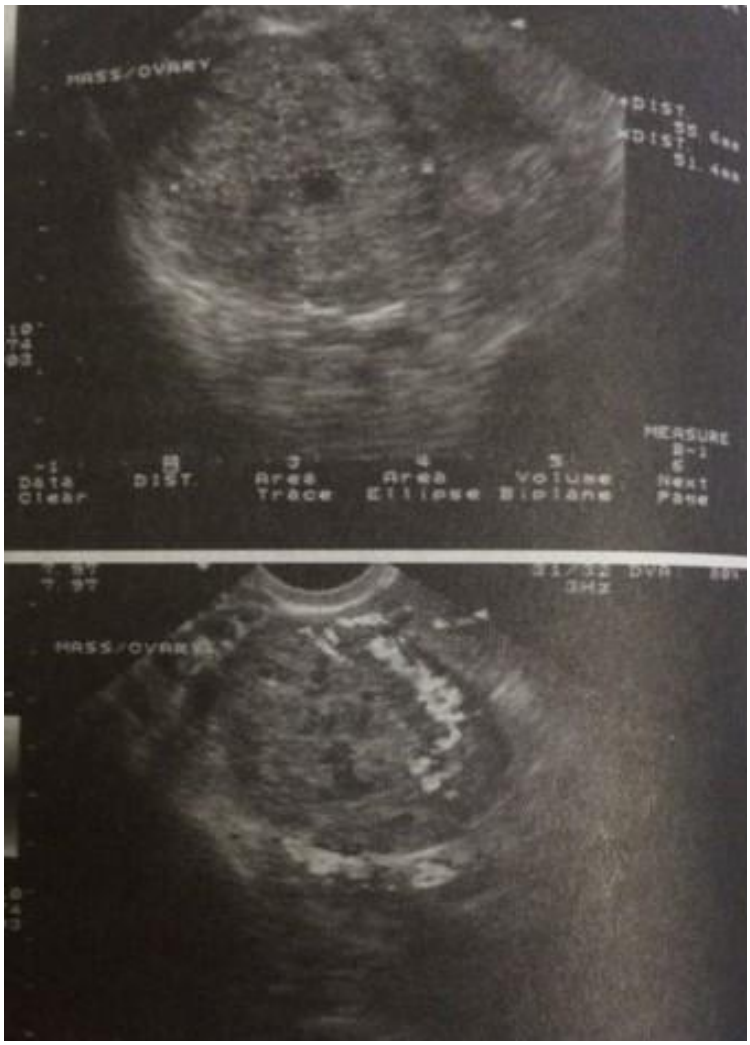


FIGURE 14 OVARIAN ECTOPIC PREGNANCY

HETEROTOPIC PREGNANCY:

A heterotopic pregnancy is diagnosed when you have any of the above types of ectopic pregnancy in conjunction with an intrauterine pregnancy[25].

FIGURE 15 HETEROTOPIC PREGNANCY

ABDOMINAL ECTOPIC PREGNANCY:

Gestational sac or trophoblastic mass separate to the uterus, fallopian tubes, and overies[26].

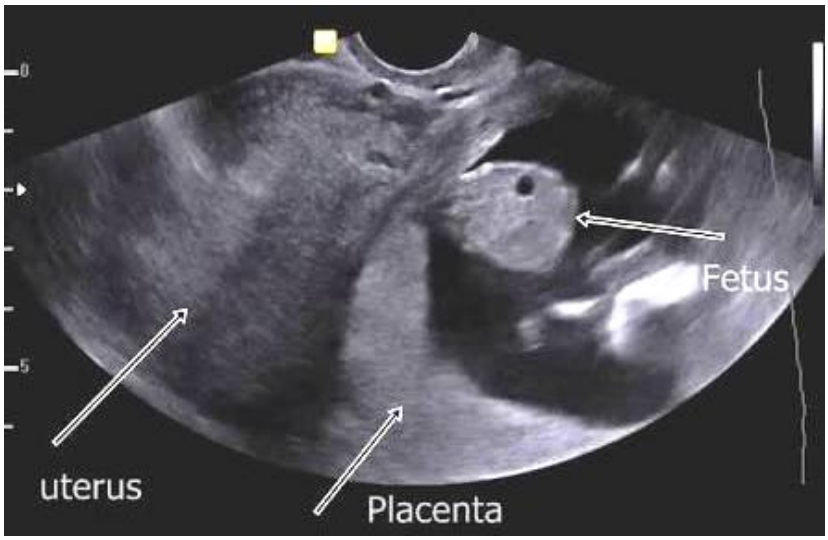


FIGURE 16 ABDOMINAL ECTOPIC PREGNANCY

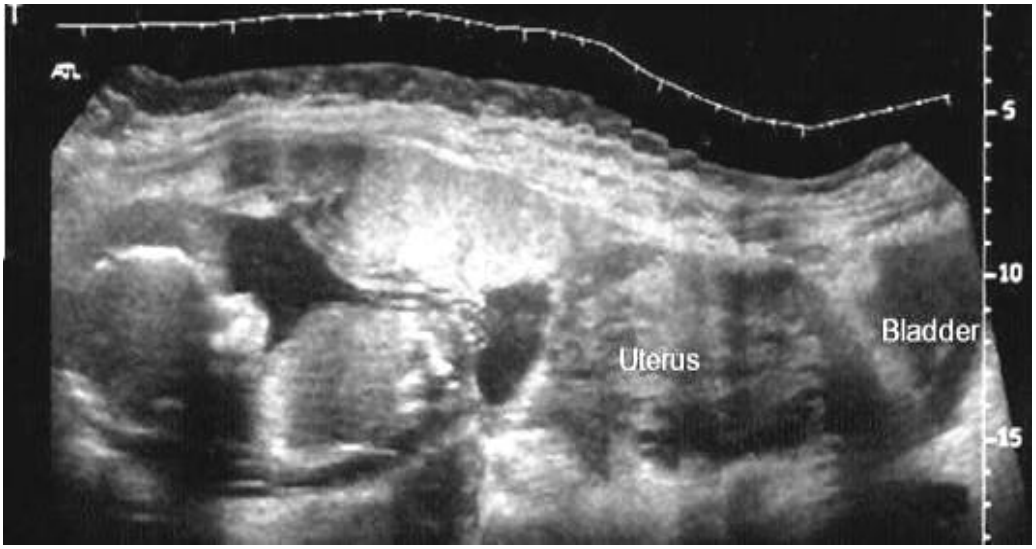


FIGURE 17 ABDOMINAL ECTOPIC PREGNANCY

PROPOSED MARKERS FOR ECTOPIC PREGNANCY BASED ON BIOLOGICAL FUNCTION[27,28].

ABORMAL IMPLANTATION.

1.Trophoblast function	hCG, PAPP – A , hPL
	Activin A , SP1.
2. Corpus luteal function	Progesterone , Inhibin A , Estradiol
	Relaxin , Renin.
3. Endometrial function	Glycodelin , Activin B,
	Leukemia inhibitory factor.

GROWTH IN FALLOPIAN TUBE.

1. Angiogenesis	VEGF
2. Muscle cell damage	Myoglobin, smooth muscle
	Heavychain , myosin , CK

3. Inflammation and Peritonel irritation	Interleukin -8, Interleukin – 6, Tumor necrosis factor alpha -	CA – 125

CK indicates creatine kinase, hCG-human chorionic gonadotropin, hPL-human placental lactogen, PAPP-A pregnancy associated plasma protein – A SPl , pregnancy – specific-1 glycoprotein, VEGF- vascular endothelial growth factor.

DIAGNOSTIC PROPERTIES OF MULTIPLE MARKER TESTS IN PREDICTING ECTOPIC PREGNANCY[29]

Biomarkers	Sensitivity	Specificity
1. IL – 6, IL – 8, and TNF	52.9%	100%
2. VEGF (PAPP-A XP)	97.7%	92.4%
3. Progesterone, VEGF, Inhibin A, activin A	98%	100%

LAPROSCOPY

Laproscopy is the standard tool for diagnosis of ectopic pregnancy. However, its routine use on all patients suspected of ectopic pregnancy may lead to unnecessary risks, cost and morbidity. Moreover, laproscopy can miss upto four percent of early EP.

Laproscopy is always indicated for patients who are haemodynamically unstable and patients with severe pain.

TREATMENT

Ectopic pregnancy can be effectively treated medically or surgically .

MEDICAL MANAGEMENT

Only methotrexate has been extensively studied as an alternate to surgical therapy. Other agents that have been used include prostaglandins;the progesterone antagonist mifepristone; traditional Chinese herbal medicines; and potassium chloride or hyperosmolar glucose injected into the ectopic mass.

The best candidate for medical therapy is a woman who is asymptomatic and motivated and who has resources to be compliant with surveillance.

METHOTREXATE

Methotrexate is a folic acid antagonist. It tightly binds to dihydrofolate reductase, blocking the reduction of dihydrofolate to tetrahydrofolate, which is the active form of folic acid. As a result, de novo purine and pyrimidine synthesis is halted, which leads to arrested DNA, RNA, and protein synthesis. Thus, methotrexate is highly effective against rapidly proliferating tissue such as trophoblast, and overall ectopic tubal pregnancy resolution rates approximate 90 percent with its use.

However, bone marrow, gastrointestinal mucosa, and respiratory epithelium can also be harmed. It is directly toxic to hepatocytes and is renally excreted. Importantly, methotrexate is a potent teratogen, and methotrexate embryopathy is notable for craniofacial and skeletal abnormalities and fetal-growth restriction . In addition, methotrexate is excreted into breast milk and

may accumulate in neonatal tissues and interfere with neonatal cellular metabolism.

Methotrexate is bound primarily to albumin, and its displacement by other medications such as phenytoin, tetracyclines, salicylates, and sulfonamides can increase methotrexate serum drug levels[30]. Moreover, renal clearance of methotrexate may be impaired by nonsteroidal antiinflammatory drugs, probenecid, aspirin, or penicillins . Last, vitamins containing folic acid may lower methotrexate efficacy.

For ease and efficacy, intramuscular methotrexate administration is used most frequently for ectopic pregnancy resolution, and single-dose and multidose methotrexate protocols are available . As noted, methotrexate can lead to bone marrow depression. This toxicity can be blunted by early administration of leucovorin, which is folinic acid and has activity equivalent to folic acid. Thus, leucovorin, which is given within the multidose protocol, allows for some purine and pyrimidine synthesis to buffer side effects.

Single-dose therapy offers simplicity, less expense, and less intensive post therapy monitoring and does not require leucovorin rescue. However, some but not all studies report a higher success rate for the multidose regimen . A third hybrid “two dose” protocol has been proposed in an effort to balance the efficacy and convenience of the two most commonly used protocols. The regimen involves administering 50 mg/m2 of methotrexate on days 0 and 4 without leucovorin rescue.

METHOTREXATE TOXICITY

Diarrhea, Nausea, vomiting, stomatitis , mucositis, renal failure, esophagitis, rash, elevated hepatic enzymes, , myelosuppression (leukopenia, thrombocytopenia, pancytopenia), hypotension, tachycardia, acute lung injury, and neurologic dysfunction (headache, depression, seizures, motor dysfunction, stroke-like symptoms, coma, encephalopathy). Toxic effects can occur hours to days or even weeks after MTX administration or overdose.

DOSAGE FOR MEDICAL MANAGEMENT

SINGLE-DOSE METHOTREXATE.

- Administer MTX 1 mg/m^2 on day 0
- Measure beta-hcg level on days 4 and 7
- If levels drop by 15%, monitor beta-hcg weekly until non pregnant level[31].
- If levels do not drop by 15%, repeat dose of MTX and measure beta-HCG on days 4 and 7.

TWO-DOSE REGIMEN.

- Administer MTX 50 mg/m^2 on days 0 and 4
- Measure beta-hcg level on days 4 and 7
- If levels drop by 15%, monitor beta-hcg weekly until non pregnant level

- If levels do not drop by 15%, repeat dose of MTX on days 7 and 11 and measure beta-HCG on days 7 and 11. If levels drop 15%, monitor beta-hcg weekly until non pregnant level.

MULTIDOSE METHOTREXATE[32].

- Administer MTX 1 mg/kg IM days 1, 3, 5, 7
- Administer leucovorin 0.1 mg/ kg days 2, 4, 6, 8
- Measure beta-hcg levels on days 1, 3, 5, 7 until 15% decrease between two measurements
- Once beta-hCG levels drop 15%, stop MTX and monitor beta-hCG weekly until non pregnant level

ABSOLUTE CONTRAINDICATIONS

❖ Hemodynamically unstable

❖ Ruptured ectopic pregnancy

- Unable to comply with medical management follow-up
- Breast feeding
- Immunodeficiency
- Alcoholism, alcoholic liver disease or chronic liver disease
- Preexisting blood dyscrasias
- Known sensitivity to methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Hepatic, renal, or hematologic disorder

RELATIVE CONTRAINDICATIONS

- Gestational sac larger than 3.5 cm.
- Embryonic cardiac motion.

MIFEPRISTONE:

It is a recently developed 19 – norsteroid with potent competitive antiprogestational and significant antiglucocoticoid as well as antiandrogenic activity. Given during the follicular phase its antiprogestin action results in attenuation of midcycle Gn surge from pituitary which results in slowing of follicular development and delay or failure of ovulation. During the luteal phase it prevents secretory changes normally brought about by progesterone. Later in the cycle it blocks progesterone support to the endometrium, unrestrains PG release from it- this stimulates uterine contactions. Mifepristone also sensitizes myometrium to PGs and indues menstruation. If implantation has occurred it blocks decidualization , conceptus is dislodged, hCG production falls, secondary luteolysis occurs- progesterone secreation decreases and cervix is softened.

Mifepristone is a partial agonist and competitive antagonist at both A anb B forms of PR. In the absence of progesterone (anovulatory cycles, after menopause) it exerts

a weak pregestational activity- induces predecidual changes. The weak agonistic action is not manifest in the presence of progesterone.

Mifepristone is active orally, but bioavailability is only 25%. It is largely metabolized in liver by CYP 3A4 and excreted in bile. Some enterohepatic circulation occurs. Half life time is 20- 36 hours. Interaction with CYP 3A4 inhibitors such as erythromycin , ketoconazole and inducers such as rifampicin and anticonvulsants have been reported.

With these properties mifepristone is generally used in termination of pregnancy , cervical ripening, postcoital contraceptive , once a month contraceptive and in induction of labour.

Recently studies suggested the usefulness of mifepristone in combination with methotrexate in termination of ectopic pregnancy. This combination regimen has found to fasten the time taken for resolution of Beta hCH and recovery.

SURGICAL MANAGEMENT

LAPAROTOMY VERSUS LAPAROSCOPY

1.There were no significant differences in overall tubal patency determined at second-look laparoscopy. This was despite higher rates of ipsilateral adhesions in the laparotomy group.

2. Each method was followed by a similar number of subsequent uterine pregnancies.

3. There were fewer repeat ectopic pregnancies in women treated laparoscopically, although this was not significant.

4. Laparoscopy resulted in shorter operative times, less blood loss, fewer analgesic requirements, and shorter hospital stays.

5. Laparoscopic surgery was significantly less successful in resolving the tubal pregnancy, however, this was balanced by the just-mentioned benefits of laparoscopy.

6. The costs for laparoscopy were significantly lower than for laparotomy, although some argue that costs are similar when cases converted to laparotomy are considered.

LAPAROSCOPY

Laparoscopy has become a recommended approach in most of the cases.

Some of the CONTRAINDICATION of laparoscopy are

- Hemodynamically unstable
- Patients with corneal ectopic pregnancy
- Multiple dense adhesions
- Massive obesity
- Massive hemoperitoneum

SALPINGOSTOMY

- This procedure is typically used to remove a small unruptured pregnancy that is usually <2 cm in length and located in the distal third of the fallopian tube.
- serum beta hCG levels >6000 mIU/ mL are associated with a higher risk of implantation into the muscularis and thus with more tubal damage.
- With surgery, a 10- to 15-mm linear incision is made on the antimesenteric border over the pregnancy.
- The products usually will extrude from the incision. These can be carefully removed or flushed out using high-pressure irrigation that more thoroughly removes the trophoblastic tissue.
- Small bleeding sites are controlled with needlepoint electrocoagulation, and the incision is left unsutured to heal by secondary intention.

FIGURE : SHOWING SALPINGOSTOMY USING DIATHERMY AND IRRIGATION.

SALPINGECTOMY

Tubal resection may be used for both ruptured and unruptured ectopic pregnancies. To minimize the rare recurrence of pregnancy in the tubal stump, complete excision of the fallopian tube is advised.

With one laparoscopic technique, the affected fallopian tube is lifted and held with atraumatic grasping forceps. One of several suitable bipolar grasping devices is placed across the fallopian tube at the uterotubal junction. Once desiccated, the tube is cut. The bipolar device is then advanced across the most proximal portion of mesosalpinx. Similarly, current is applied, and the desiccated tissue cut. This process moves serially from the proximal mesosalpinx

to its distal extent under the tubal ampulla. Alternatively, an endoscopic suture loop can be used to encircle and ligate the knuckle of fallopian tube that contains the ectopic pregnancy and its underlying vascular supply within the mesosalpinx.

Two consecutive suture loops are placed, and the tube distal to these ligatures is then cut free with scissors.

Most tubal ectopic pregnancies are small and pliant. Accordingly, they can be held firmly by grasping forceps and drawn up into one of the accessory site cannulas. Larger tubal ectopic pregnancies may be placed in an endoscopic sac to prevent fragmentation as they are removed through the laparoscopic port site.

Importantly, to remove all trophoblastic tissue, the pelvis and abdomen should be irrigated and suctioned free of blood and tissue debris. Slow and systematic movement of the patient from Trendelenburg to reverse trendelenburg positioning during irrigation can also assist in dislodging stray tissue and fluid. These should be suctioned and removed from the peritoneal cavity.

EXPECTANT MANAGEMENT

In select cases, it is reasonable to observe very early tubal pregnancies that are associated with stable or falling serum Beta hCG levels[33]. As many as one third of such women will present with declining Beta hCG levels. Expectant management is restricted to women with tubal ectopic pregnancies only, decreasing serial Beta hCG levels, diameter of the ectopic mass ≤ 3.5 cm, and no evidence of intra abdominal bleeding or rupture by transvaginal sonography. Almost one third of tubal ectopic pregnancies measuring < 3 cm and with β-hCG levels < 1500 mIU/mL resolved without intervention[34]. Eighty eight percent of ectopic pregnancies will resolve if the Beta-hCG is < 200 mIU/mL.

With expectant management, subsequent rates of tubal patency and intrauterine pregnancy are comparable with surgery and medical management. The potentially grave consequences of tubal rupture, coupled with the established safety of medical and surgical therapy, require that expectant therapy be undertaken only in appropriately selected and counseled women.

AIM

To compare the efficacy of mifiprestone in combination with methotrexate vs methotrexate alone for medical management of ectopic pregnancy.

PERIOD OF STUDY

2 years.

STUDY DESIGN

Prospective and retrospective comparative study.

INCLUSION CRITERIA

- Haemodynamically stable patients.
- Sac size less than 4cm on usg.
- Beta HCG < 10,000mIU/ml.
- Absent cardiac activity in the sac.

- Patient willing for follow up.

EXCLUSION CRITERIA

- Haemodynamically unstable patients
- Ectopic of diameter greater than 4 cm on usg
- Patients with hepatic and renal dysfunction
- Smokers over the age of 35 yrs
- Long term corticosteroid users
- Patients with hemorrhagic disorder on anticoagulant
- Patients who did not consent

MATERIAL AND METHOD

- 20 patients with ectopic pregnancy full filling the criteria of medical management will be chosen and given a single dose of 200 mg mifepriostone along with single im injection of methotrexate 50mg/sq.m body surface area.

- Baseline serum beta HCG level, UPT and USG will be done for all pts, detailed history of symptoms and past medical h/o will be recorded, examination findings and vital parameters recorded. Complete haemogram, renal function tests and liver function test also done for all patients.

- Following treatment women will be reviewed on day 4 and day 7

- All women had beta HCG estimations hepatic and renal function tests and full blood count on each visit

- If the HCG concentration dropped by more than 15% between day 4 to 7 the women will then be reviewed weekly until the HCG concentrations were below 12IU/L.

- If the decrease was less than 15% between day 4 to 7 then a second dose of methotrexate will be administered.

- In these cases blood HCG concentrations will be estimated also on day 11 and 14.

- The results of the combination therapy will be compared retrospectively with patients treated with single dose i.m methotrexate alone in the past.

COMPARISON CRITERIA

- Resuts will be compared based on the following criteria

- Time interval between drug administration and complete resolution

- No of pts requiring 2nd dose methotrexate

- No of pts undergoing laprotomy due to haemodynamic instability and worsening of symptoms

PROFORMA

Name Age/sex

Occupation Social status

Address

Date of admission Date of discharge

I p no

Presenting complaints

Menstrual h/o

Marital h/o

Obs h/o

LMP

Past h/o

Family h/o

Personal h/o

General examination

Systemic examination CVS RS CNS

P/A

L/E P/S: P/V

INVESTIGATION

	Day 0	1st week		2nd week		3rd week	4th week	5th week	6th week
		Day 4	Day 7	Day 11	Day 14				
USG									
Beta HCG									
Hb									
PCV Sr Urea /creatin									

	Day 0	1st week		2nd week		3rd week	4th week	5th week	6th week
Sr bilirubin		Day 4	Day 7	Day 11	Day 14				
SGOT SGPT									

No of doses of methotrexate injection:

If case taken for laprotomy:

Time taken for beta HCG to normalize:

Duration of hospital stay:

Improvement of symptoms:

Worsening of symptoms:

RESULT

- 20 cases where treated with mefipristone and methotrexate combination.
- Out of which 17 cases resolved completely which is 85% success.
- Three patients needed laprotomy due to failure of medical management which is 15%.
- Three patients needed second dose of methotrexate.
- The average time taken for complete resolution 21 days.
- The average duration of hospital stay 7 days.
- Results where compared retrospectively with 20 patients with methotrexate alone.
- Out of these 14 cases resolved completely with medical management which account to 70% success rate.
- Six cases needed emergency laprotomy 30% failure rate.

- Five cases needed second dose of methotrexate.

- The average time taken for complete resolution is 28 days.

- Average duration of hospital stay 12 days.

ANALYSIS OF RESULTS

ANALYSIS OF STUDY

Chi-sqare statistic is 1.2903 and p value Is 0.255989 which was not significant statistically at $p<0.05$. Thus the combination of mifepristone and methotrexate in medical management was not statistically significant.

	SUCCESS	FAILURE
MIFEPRISTONE AND METHOTREXATE COMBINATION	17	3
METHOTREXATE ONLY	14	6

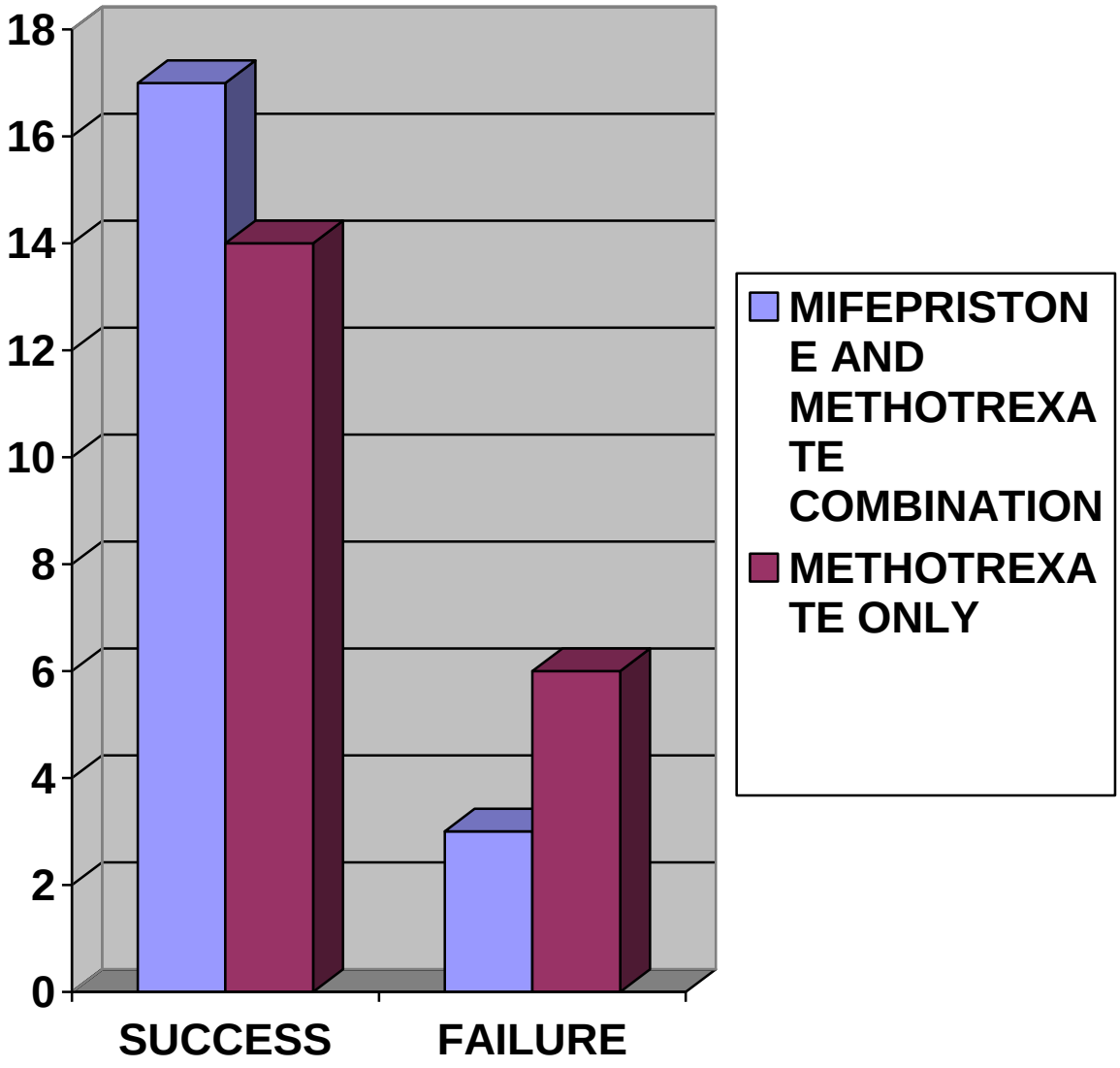


FIGURE 1 : BAR CHART SHOWING SUCCESS AND FAILURE RATE OF THE STUDY

SECOND DOSE OF METHOTREXATE

The chi-square statistic is 1.3089 and p value is 0.252595 which was not significant at $p < 0.05$. Thus the combination drugs did not prevent the requirement of the second dose of methotrexate.

	2 DOSE METHOTREXATE	1 DOSE METHOTREXATE
MIFEPRISTONE AND METHOTRXATE COMBINATION	3	14
METHOTREXATE ONLY	5	9

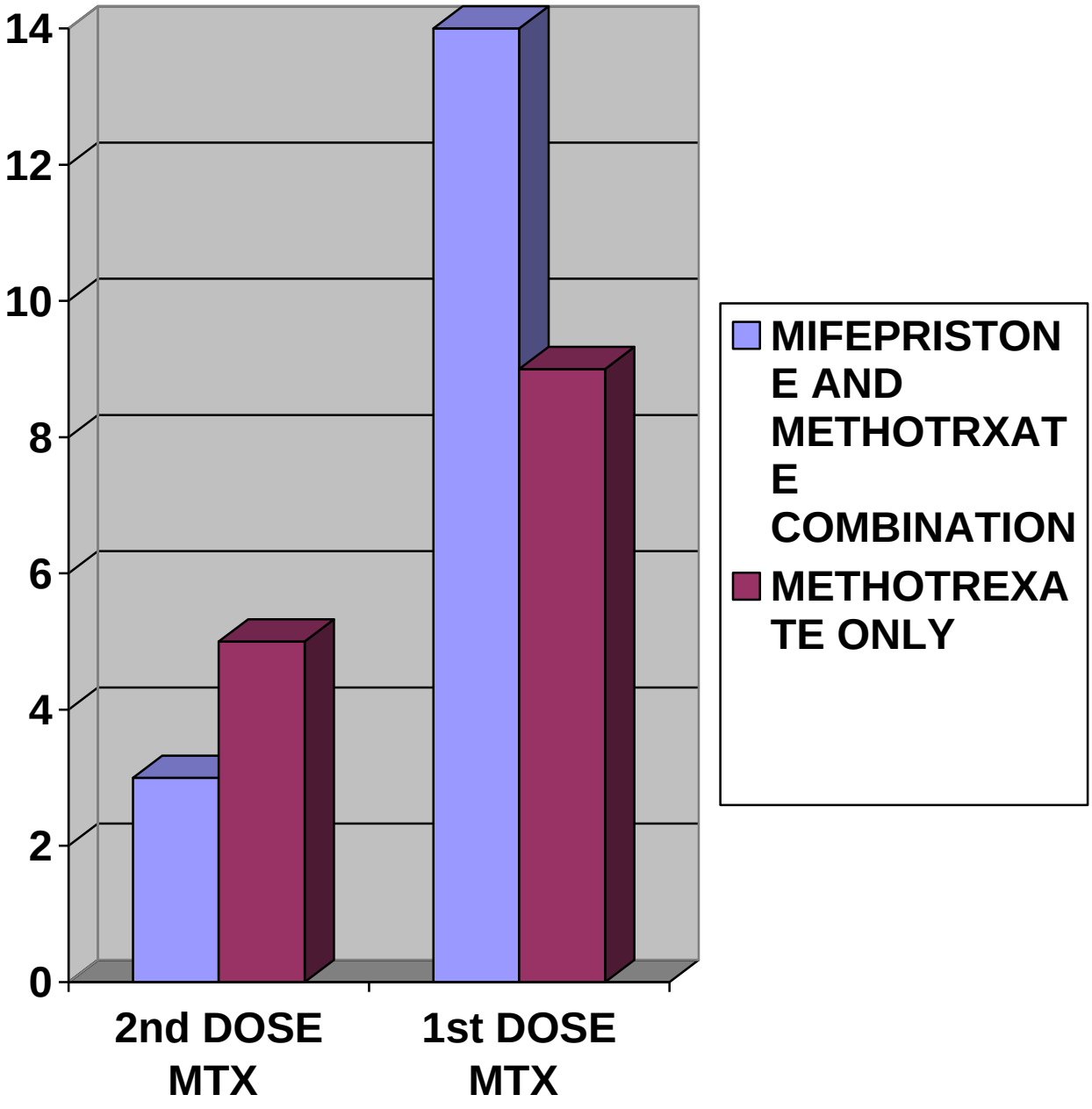


FIGURE 1 : BAR CHART SHOWING THE USE OF SECOND DOSE OF METHOTREXATE IN OUR STUDY

TIME TAKEN FOR RESOLUTION

The chi-square statistic is 9.3136. The p value is 0.002275. The result is significant at $p < 0.05$. Thus the combination drugs effectively reduced the time taken for Beta HCG to normalize.

	<= 3 WEEKS	> 3 WEEKS
MIFEPRISTONE AND METHOTREXATE COMBINATION	13	4
METHOTREXATE ONLY	3	11

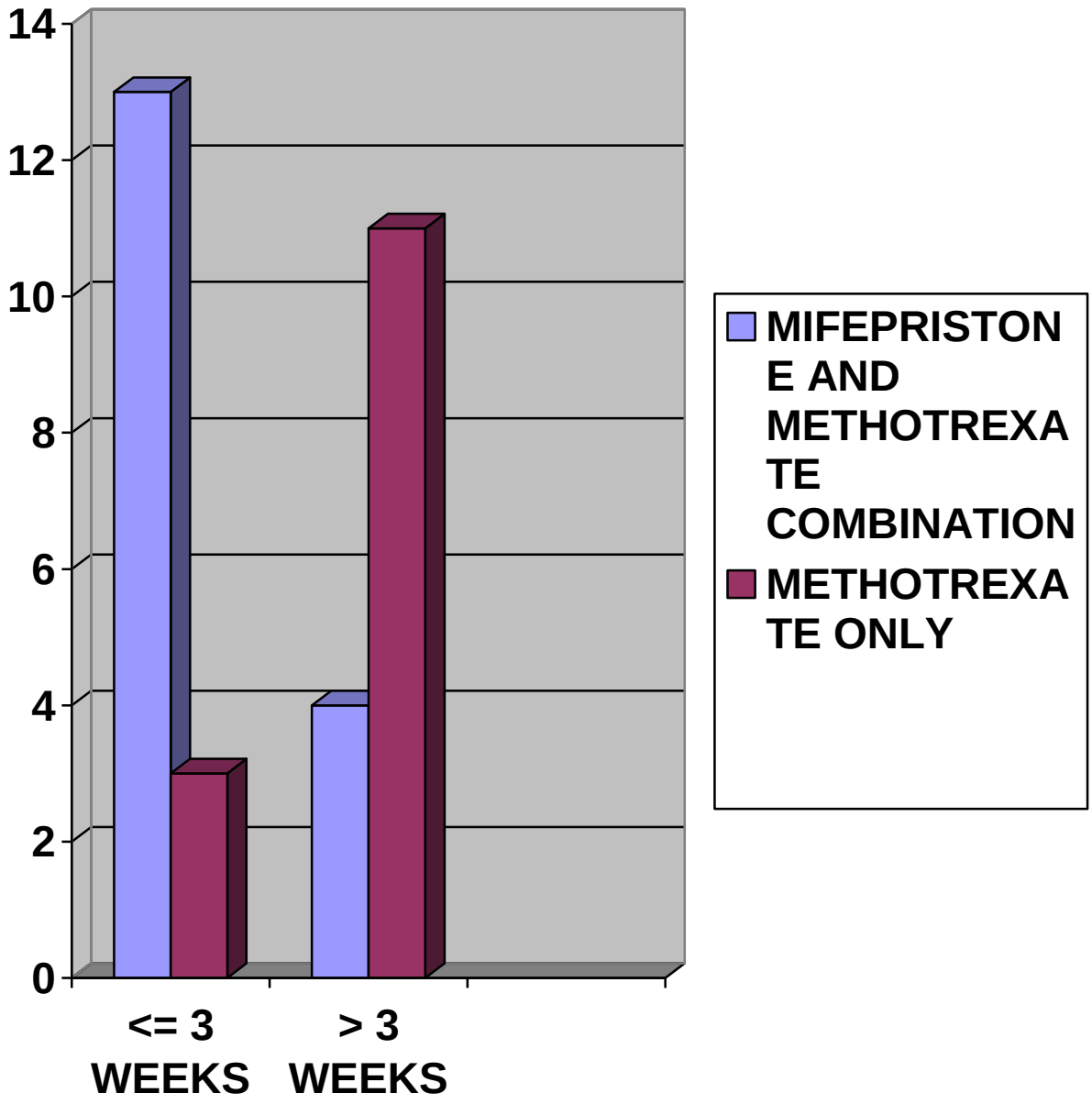
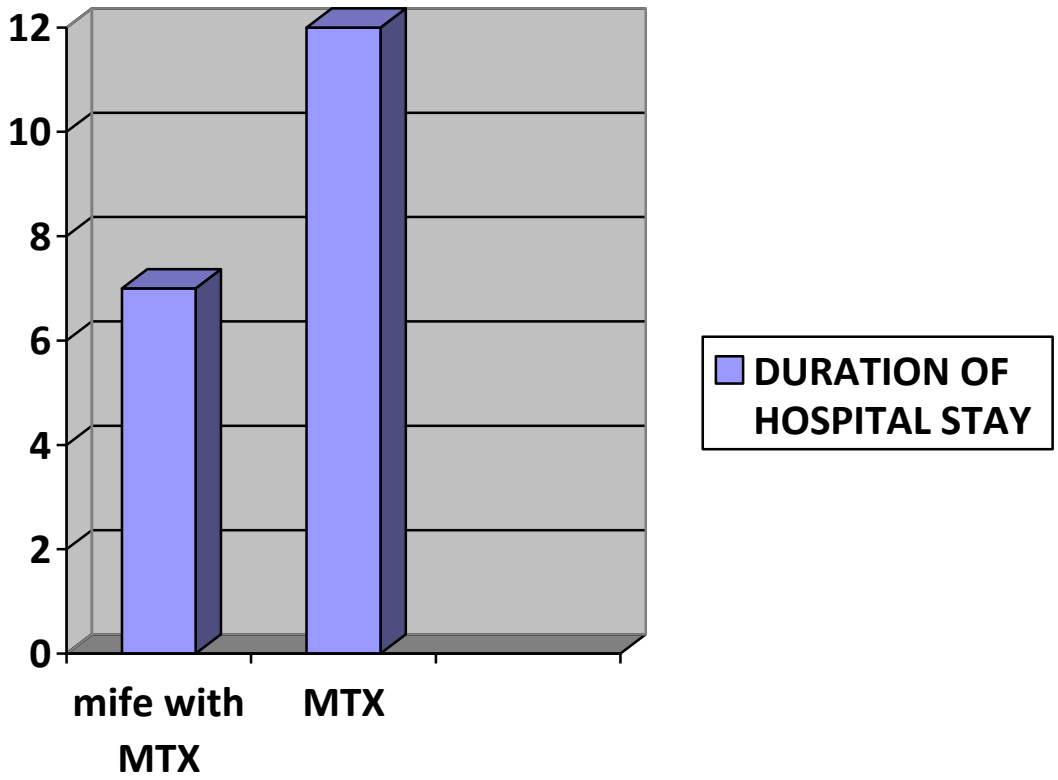


FIGURE 2 : BAR CHART SHOWING THE TIME TAKEN FOR RESOLUTION OF BETA HCG IN THE STUDY

DURATION OF HOSPITAL STAY

- The average duration of hospital stay was 7 days for cases treated with combination of mifepristone and methotrexate.

- The average duration of hospital stay was 12 days in cases treated with methotrexate alone.



SUMMARY

In my study with a sample size 40, 20 patients were treated with methotrexate 50 mg/m2 and mifepristone 200mg and the results were compared retrospectively 20 patients treated with methotrexate 50mg/m2 alone in the past

The cases and controls were matched with respect to age and gravidity.

CASES

Age	19-32 years
Primi gravida	11 patients
Second & multigravida	9 patients
Baseline beta hCG range	1500- 3300IU
Weeks of gestation	5 -7 weeks
Sac size range	0.6 -3 cm

ETIOLOGICAL RISK FACTORS IDENTIFIED AMONG CASES

- Two patients had past history of leucorrhea and treated for the same.
- One patient had conceived after sterilization.
- One patient had conceived after ovulation induction with intra uterine insemination.

CONTROL

Age	20- 33 years
Primi gravida	10 patients
Second & multigravida	10 patients
Baseline beta hCG range	1500-3200IU
Weeks of gestation	5 -7 weeks
Sac size range	0.6 -3 cm

ETIOLOGICAL RISK FACTORS IDENTIFIED AMONG CONTROL

- Three patients had past history of leucorrhea and treated for the same.
- One patient had conceived after tubal re anastomosis.
- One patient had conceived with intra uterine device in situ.
- Two patients had conceived after ovulation induction.

Both cases and control fulfilled the criteria for medical management of ectopic pregnancy.

✓ Out of the 20 patients in the case study group 17 cases resolved completely with a success rate of 85 %.

✓ 3 patients needed laprotomy due to failure of medical management which was 15%.

✓ These patients had tachycardia and worsening of pain and hypotension for which laprotomy was done.

- ✓ All 3 patients had ruptured ectopic with haemoperitoneum on laprotomy.

- ✓ 3 patients needed a second dose of methotrexate because the fall in beta HCG was <15% between day 4 and day 7.

- ✓ The average time taken for complete resolution was 21 days.

- ✓ The average duration of hospital stay was 7 days.

The results were compared retrospectively with 20 patients treated with methotrexate alone in the past.

- ✗ Out of these 14 cases resolved completely with a success rate of 70%.

- ✗ 6 patients needed emergency laprotomy due to tachycardia and haemodynamic instability.

    - In 5 patients ruptured ectopic and haemoperitoneum .

    - 1 patient had worsening of pain and tachycardia and on laprotomy no rupture was seen.

- Hence the failure rate was 30%.

- 5 cases needed a second dose methotrexate due to <15% fall in Beta HCG between day 4 and day7 which was 25%.

- Average time taken for complete resolution was 28 days.

- Average duration of hospital stay was 12 days.

CONCLUSION

This study done in our hospital compared the efficacy of methotrexate with mifepristone in combination Vs methotrexate alone in medical management of ectopic pregnancy. The results were compared based on the success rate , patients needing second dose methotrexate , time taken for complete resolution and average duration of hospital stay.

- The combination of methotraxate and mefepristone gave a success rate of 85% as against methotrexate alone which had only 70% success rate. On applying chi square test and P value was 0.255989 and hence this was not statistically significant.

- 15 percent of patients in combination group needed a second dose of methotrexate as against 25% in the control group. On applying chi square test P value was 0.252595 which was also not statistically significant.

- 65 percent patients Beta HCG in the combination group resolved < 3 weeks as compared to 15 % in the methotrexate alone group. on applying chi square test P value was 0.002275 . Result was significant as P value is less than 0.05.

- The average duration of hospital stay was five days less in the combination group than cases treated with methotrexate alone.

According to my study, there is earlier resolution of ectopic pregnancy and reduced duration of hospital stay when combination of mifepristone and methotrexate is used as compared to methotrexate alone for medical management.

Larger studies are needed to prove the effectiveness of the combination group in terms of success rate.

REVIEW OF LETERATURE

- Marc perdu and erick camus 98 conducted a non randomised study. Results were of the 30 pts treated with the combination there was only 1 failure were as treatment had failed in 11 out of the 42 patients treated with mtx alone.Hence concluded that combination therapy reduced the risk of failure of medical management. AJOG 1998.

- Gazvani and baruah 1987, at liverpool hosp u.k conducted a RCT. 25 patients in each group.results were unruptured ectopic pregnancy resolved faster in patients treated with mife and mtx rather than mtx alone. The effect was more pronounced in women with higher hcg concentrations.

- Li ZH and Quan S conducted a study in 2004 in china to observe the effects of mifepristone combined with methotrexate for conservative treatment of tubal pregnancy. A total of 102 cases received mefiprestone 600mg and methotrexate

1 mg /kg wt compared to 86 cases of single dose methotrexate. Curative rate was 92% in combined therapy when compared 81% in single dose therapy.

- Gomez Garcia MT and Aguaron Benitez G conducted a study to describe cases of cervical or interstitial ectopic pregnancy managed conservatively with combined medical treatment (methotrexate and mifepristone) alone or in association with other minimally invasive strategies.

All patients were successfully treated and had no adverse reactions with intramuscular methotrexate50 mg/m² and oral mifepristone 600 mg, either alone or in association with minimally invasive treatment (uterine artery embolization and evacuation dilation and curettage). All patients remained asymptomatic with β-HCG levels that decreased and became negative within 14-49 days: the median hospital stay was 5.5 days. We also describe the first patient with a cervical ectopic pregnancy treated with methotrexate and mifepristone, followed by vaginal misoprostol 800 mcg for cervical evacuation.

Methotrexate - mifepristone, either alone or in combination with other minimally invasive strategies, could be considered an option for the treatment of both cervical and interstitial ectopic pregnancy. An individualized approach should be used in each patient, however, given the wide variety of possible clinical situations and the potential seriousness of ectopic pregnancy.

- Song HD and Chen SL conducted a study to evaluate the clinical effect and safety of combined use of methotrexate and mifepristone for treatment of ectopic pregnancy.

Twenty-three randomized controlled trials involving totally 1 706 patients were collected according to the inclusion criteria, and meta-analysis of the data indicated that combined use of methotrexate and mifepristone can be of great value in the management of ectopic pregnancy in comparison with exclusive use of methotrexate [combined odds ratio (OR) was 2.84 with 95%confidence interval [CI] (2.18, 3.69), Z=7.79, P<0.000 01].

The clinical evidence derived from the analysis suggests that the combination of methotrexate and mifepristone for ectopic pregnancy management can be effective with good safety security and minimal side effects, but still, this conclusion needs further verification by randomized, double-blind, and controlled trials with larger sample size and more rigorous trial design.

- Chevret S and Camus E conducted a study to prove the increase in the efficacy of methotrexate with the association of mifepristone in the medical management of ectopic pregnancy.

A total of 212 ectopic pregnancies was randomized. There was no significant difference in the initial characteristics between the two groups. There was no significant difference in the success rate of medical treatment between the methotrexate-mifepristone (n = 113) and the methotrexate-placebo group (n = 99): 79.6% (90/113) versus 74.2% (72/97) respectively, RR (95% CI): 1.07 (0.92-1.25), P = 0.41, non-significant. However, there was a quantitative interaction between progesterone level and effect of treatment: when progesterone level

was >/=10 ng/l, the efficacy of the combination of mifepristone and methotrexate was significantly higher than the combination of methotrexate and placebo, with an 83.3% success rate (15/18) versus 38.5% (5/13) respectively.

This study failed to demonstrate any benefit of the addition of mifepristone to methotrexate. By contrast, the quantitative interaction between treatment effect and baseline serum progesterone suggested that this combination could be limited to ectopic pregnancies associated with high serum progesterone concentrations.

BIBILIOGRAPHY

1. Golditch IM. Lawson Tait : the forgotten gynecologist. Obstet Gynecol. 2002, 99 : 152 – 156
2. Antunes ML, Delascio D.Immunological diagnosist of pregnancy by the anti – HCG serum test. Matern Inface. 1966, 25:725, 732
3. Kobayashi M.Hellman LM, Fillisti LP.Ultrasound. An aid in the diagnosis of ectopic pregnancy. Obster Gynecol.1969, 103:1131-1140.
4. Veena P.Use of mifepristone along with methotrexate in medical management of unruptured ectopic pregnancy. J Obster Gynaecol. 2011, 31 : 667
5. Kamwendo F, Forslin L, Bodin L, et al. Epidemiology of ectopic pregnancy during a 28 year period and the role of pelvic inflammatory disease. Sex Transm Infect, 2000, 76 : 28 – 32
6. Cagnacci A, Landi S, Volpe A. Rhythmic variation in the rate of ectopic pregnancy throughout the year. Am J Obstet Gynecol. 1999, 180 : 1067 – 1071

7. Shaw JL, Wills GS, Lee KF, et al. Chlamydia trachomatis infection increases fallopian tube PROKR2 via TLR2 and NFKB activation resulting in a microenvironment predisposed to ectopic preganancy. AM J Pathol. 2011, 178 : 253 – 260.
8. Creanga AA, Shapiro – Mendoza CK, Bish CL, et al, Trends in ectopic pregnancy mortality in the United State, 1980 – 2007, Obstet Gyneclo. 2011, 117 : 837 – 843
9. Mol BW, Hajenius PJ. Engelsbel S, et al. Can noninvasive diagnostic tools predict tubal rupture or active bleeding in patients with tubal pregnancy? Fertil Steril. 1999, 71 : 167 – 173.
10. Senterman M.Jibodh R, Tulandi T.Histopathologic study of ampullary and isthmic tubal ectopic pregnancy. Am J Obstet Gynecol. 1988, 159 : 939 – 941
11. Barnhart KT, Sammel MD, Rinaudo PF, et al. Symptomatic partients with an early viable intrauterine pregnancy, HCG curves redefined. Obstet Gynecol 2004, 104 : 50 – 55
12. Daya S.Human chorionic gonadotropin increase in normal early pregnancy. Am J Obstet Gynecol 1987, 156 : 286 – 290

13. Kadar N, Freedman M, Zacher M.Further observations on the doubling time of human chorionic gonadotropin in early asymptomatic pregnancies. Fertil Steril 1990, 54 : 783 – 787

14. Bernaschek G, Rudelstorfer R, Csaicsich P.Vaginal sonography versus serum human chorionic gonadotropin in early detection of pregnancy. Am J Obstet Gynecol. 1988, 158 : 608 – 612

15. Kirk E, Papageorghiou AT, Condous G, et al. The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. Hum Reprod 2007, 22 : 2824 – 2828

16. Atri M, Valenti DA, Bret PM, et al. Effect of transvaginal sonography on the use of invasive procedures for evaluating patients with a clinical diagnosis of ectopic pregnancy. J Clin Ultrasound. 2003, 31 : 1 – 8.

17. Braffman BH. Coleman BG, Ramchandani P, et al. Emergency department screening for ectopic pregnancy, a prospective US study. Radiology 1994, 190 : 797 – 802.

18. Barnhart KT, Simhan H, Kamelle SA, Diagnostic accuracy of ultrasound above and below the beta – h CG discriminatory zone. Obstets Gynecol. 1999, 94 .

19. Winder S.Reid S.Condous G. Ultrasound diagnosis of ectopic pregnancy. Aust J. Ultrasound Med. 2011, 14 : 29 – 33.

20. Tanaka T.Hayashi H.Kutsuzawa T.et al Treatment of interstitial ectopic pregnancy with methotrexate, report of a successful case. Fertil Steril. 1982, 37: 851 – 852.

21. Winder S.Reid S.Condous G. Ultrasound diagnosis of ectopic pregnancy. Aust J. Ultrasound Med. 2011, 14 : 29 – 33.

22. Seow K.M. Huang LW, Lin YH, et al, Cesarean scar pregnancy, issues in man agement, Ultrasound Obstet Gynecol. 2004, 23 : 247 – 253.

23. Michencer. C.Dickinson JE. Caesarean scar ectopic pregnancy, a single centre case series. ANZJOG, 2009, 49 : 451 – 455.

24. Grimes HG, Nosal RA, Gallagher JC. Ovarian pregnancy, a series 24 cases. Obstet Gynecol. 1983, 61 : 174 – 180.

25. Barrenetxea G, Barinaga – Rementeria L, Lopez de Larruzea A, et al, Heterotopic pregnancy, two cases and a comparative review. Fertil Steril 2007, 87 : 417 – e9 – 417. e 15

26. Condous G.Timmerman D, Goldstein S, et al. Pregnancies of unknown location, a consensus statement. Ultrasound Obstet Gynecol. 2006, 28 : 121 – 122.

27. Bonassi S, Neri M, Puntoni R Validation of biomarkers as early predictors of disease. Mutat Res. 2001, 480 – 481: 349 – 349

28. Cartwright J. Duncan WC, Critchley HO, et al Serum biomarkers of tubal ectopic pregnancy, current candidates and future possibilities. Reproduction 2009, 138 : 9 – 22.

29. Soriano D. Hugol D.Quang NT, et al. Serum concentrations of interleukin – 2R (IL – 2R), 1L – 6, 1L8, and tumor necrosis factor alpha in patients with ectopic pregnancy. Fertil Steril. 2003, 79 : 975 – 980.

30. Breedveld P, Zelcer N, Pluim D, et al, Mechanism of the Pharmacokinetic interaction between methotrexate Res 2004, 64 : 5804 – 5811.

31. ACOG Practice Bulletin No.94, Medical management of ectopic pregnancy. Obstet Gynecol 2008, 111 : 1479 – 1485.

32. Barnhart KT, Gosman G, Ashby R, et al. The medical management of ectopic pregnancy, a meta – ananlysis comparing “single dose” and “multidose” regiments. Obstet Gynecol 2003, 101, 778 – 784.

33. Cohen MA, Sauer MV, Expectant management of ectopic pregnancy. Clin Obstet Gynecol. 1999, 42 : 48 -54

34. Mol BW, Van der Veen F, Results of expectant management of women early pregnancy and unknown location Ultrasound Obstet Gynecol 2000, 15 : 265

CASES GROUP : MIFEPRISTONE 200mg + METHOTREXATE 50mg/m^2

S NO	NAME	AGE/ SEX	GRAVIDA	GESTATIONAL AGE	SAC SIZE	BASELINE BETA HCG	FINAL BETA HCG	NO OF MTX DOSES	TIME TAKEN FOR BETA HCG TO NORMALISE	DURATION OF STAY	WORSENING OF SYMPTOMS	LAPROTOMY NEEDED
1	Vijaya	32	G2P1L1	5w	0.9x1cm	1900	12	1	3 weeks	7 days	No	No
2	sumathy	30	PRIMI	5w+5d	1.2x1cm	2100	10	1	3 weeks	6 days	No	No
3	Uma ranjini	28	PRIMI	5w+1d	0.8x0.9cm	1860	12	1	3 weeks	7 days	No	No
4	Meera	21	PRIMI	5w+6d	0.9x0.7cm	2640	Nd	1	3 weeks	8 days	Yes	Yes
5	Santhakumari	22	PRIMI	5w+5d	1.0x0.7cm	1916	10	1	3 weeks	9 days	No	No
6	Kumutha	23	PRIMI	6w+2d	1.9x1.5cm	1514	13	2	3 weeks	7 days	No	No
7	Kumuthavalli	24	G3A2	6w+6d	2.3x2cm	1714	10	1	4 weeks	7 days	No	No
8	Anbulakshmi	25	PRIMI	5w+5d	1.2x1cm	3212	12	2	4 weeks	7 days	No	No
9	Vijayalakshmi	28	G3P1L1A1	5w+2d	1x0.9cm	2814	Nd	1	4 weeks	8 days	No	No
10	Rupavathy	30	PRIMI	5w+5d	1.1x0.7cm	2112	10	1	2 weeks	7 days	Yes	Yes

S NO	NAME	AGE/ SEX	GRAVIDA	GESTATIONAL AGE	SAC SIZE	BASELINE BETA HCG	FINAL BETA HCG	NO OF MTX DOSES	TIME TAKEN FOR BETA HCG TO NORMALISE	DURATION OF STAY	WORSENING OF SYMPTOMS	LAPROTOMY NEEDED
11	Rose	19	PRIMI	5w+3d	1.2x0.9cm	2914	13	2	2 weeks	7 days	No	No
12	Nathiya	22	G2P1L1	6w+4d	2.3x1.9cm	1916	15	1	2 weeks	6 days	No	No
13	Dhanalakshmi	28	G2P1L1	5w+1d	0.9x0.6cm	1614	9	1	3 weeks	7 days	No	No
14	Lakshmi	22	G3A2	5w	0.7x0.9cm	1836	Nd	1	4 weeks	7 days	No	No
15	Saritha	24	PRIMI	5w+4d	1.0x0.8cm	3115	11	1	3 weeks	7 days	Yes	Yes
16	Goshalaya	32	PRIMI	5w+5d	0.8x0.6cm	1800	10	1	4 weeks	8 days	No	No
17	Devi	28	G2P1L1	5w	0.9x0.6cm	2146	9	1	3 weeks	7 days	No	No
18	Saritha	26	G2P1L1	5w	1.0x0.8cm	3000	8	1	3 weeks	7 days	No	No
19	Vedhakumari	26	G3P1L1A1	5w+1d	1.1x0.7cm	2100	10	1	4weeks	7 days	No	No
20	Priyanka	22	PRIMI	6w+6d	2.5x2.3cm	1513	nd	1	2weeks	7 days	No	No

CONTROL GROUP : METHOTREXATE 50mg/m^2ALONE

S NO	NAME	AGE/ SEX	GRAVIDA	GESTATIONAL AGE	SAC SIZE	BASELINE BETA HCG	FINAL BETA HCG	NO OF MTX DOSES	TIME TAKEN FOR BETA HCG TO NORMALISE	DURATION OF STAY	WORSENING OF SYMPTOMS	LAPROTOMY NEEDED
1	Kalai	28	G2A1	5W+5D	0.8 x1cm	2914	ND	1	3 weeks	11 DAYS	YES	YES
2	Emishella	22	PRIMI	5W+5D	0.6 x 0.8cm	3118	ND	1	3 weeks	11 days	Yes	Yes
3	Bismi rose	24	PRIMI	5w+3d	0.8 x 1cm	3140	Nd	1	4 weeks	14 days	No	No
4	Gowsalya	30	G2P1L1	5w	0.7 x 1 .1cm	2114	7	1	4 weeks	11 days	No	No
5	Sudha	28	PRIMI	6w+2d	1.6 x 1.8cm	1953	5	1	4 weeks	11 days	No	No
6	Rajiyabee	30	G3P1L1A1	5w+1d	1.1 x 0.9cm	1864	13	1	4 weeks	14 days	No	No
7	Famidha	26	G2A1	5w+1d	1 x 0.8cm	1930	14	1	4 weeks	14 days	No	No
8	Kaveri	20	PRIMI	5w+5d	0.9 x 0.8cm	2916	13	2	5 weeks	21 days	No	No
9	Surekha	24	PRIMI	5w	0.9 x 0.7cm	2863	6	2	4 weeks	14 days	No	No
10	Veeralakshmi	32	G2P1L1	6w +4 d	2.2 x 1.9cm	1860	6	1	4 weeks	11 days	No	No

S NO	NAME	AGE/ SEX	GRAVIDA	GESTATIONAL AGE	SAC SIZE	BASELINE BETA HCG	FINAL BETA HCG	NO OF MTX DOSES	TIME TAKEN FOR BETA HCG TO NORMALISE	DURATION OF STAY	WORSENING OF SYMPTOMS	LAPROTOMY NEEDED
11	Eromia	24	PRIMI	6w+ 6 d	2.3 x 1.9cm	1412	12	2	3 weeks	11 days	No	No
12	Shanthi	33	G2P1L1	5w+ 5d	1.2 x 1cm	3214	11	2	5 weeks	14 days	No	No
13	Halithamal	23	G2P1L1	6w+ 6d	1.8 x 1.5cm	2160	12	1	3 weeks	14 days	No	No
14	Sumadevi	25	PRIMI	5w+2d	1.1 x 0.8cm	1550	9	1	4 weeks	10 days	No	No
15	Sakaligiri	23	PRIMI	5w+3d	1.2 x 0.9cm	2314	Nd	1	4 weeks	11 days	Yes	yes
16	Divya	21	PRIMI	5 w	0.8 x 0.6cm	1914	12	1	5 weeks	10 days	No	No
17	Remya	26	G3P1L1A1	6w+ 6d	2.4 x 2.1cm	2198	10	2	4 weeks	14 days	No	No
18	Usha	23	PRIMI	5w + 6d	1.2 x 0.9cm	2112	Nd	1	3 weeks	14 days	Yes	yes
19	Kokila	22	G2A1	5w+ 3d	1.1x 0.8cm	2640	Nd	1	5 weeks	9 days	Yes	Yes
20	Rani	26	G2P1L1	6 w + 6 d	2.5x 2.2cm	3115	nd	1	4 weeks	9 days	yes	Yes

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.Niveditha V.C.
Postgraduate M.S.(Obstetrics & Gynaecology)
Madras Medical College
Chennai 600 003

Dear Dr.Niveditha V.C.

The Institutional Ethics Committee has considered your request and approved your study titled **"A Comparative study on the efficacy of methotrexate and combination of mifepristone with methotrexate for medical management of ectopic pregnancy" No.08012015.**

The following members of Ethics Committee were present in the meeting held on 20.01.2015 conducted at Madras Medical College, Chennai-3.

1.	Dr.C.Rajendran, M.D.,	: Chairperson
2.	Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3.	Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4.	Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5.	Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6.	Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7.	Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
8.	Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9.	Thiru S.Rameshkumar	: Lay Person
10.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
11.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee

Information to Participants

Title : Comparative study of efficacy of Methotrexate and Mifepristone with Methotrexate in the Medical Management of Ectopic pregnancy

Principal Investigator : **Dr. Niveditha**

Name of Participant :

Site : **IOG, Egmore, Chennai-8.**

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

To compare the efficacy of Methotrexate and Mifepristone with Methotrexate in the Medical Management of Ectopic pregnancy.

We have obtained permission from the Institutional Ethics Committee.

The study design

It is a prospective and retrospective comparative study. All patients in the study will be given Methotrexate and Mifepristone and results compared with patients treated in the past.

Study Procedures

The study involves evaluation of efficacy of Mifepristone with Methotrexate combination in medical management of ectopic pregnancy for which we will be monitoring your USG, CBC, RFT, LFT and β-HCG. The planned schedule visits involves visit at 4^{th} and 7^{th} day of treatment after your initial visit. If needed you will be reviewed on 11^{th} and 14^{th} day and then once weekly till your β-HCG levels fall below 12 mIU.

Possible risk to you

You might need emergency surgery in case of treatment failure.

Possible benefits to you

Your condition could respond better and resolve faster with the combination treatment.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator

Date

Signature of Participant

Date

INFORMED CONSENT FORM

Title : Comparative study of efficacy of Methotrexate and Mifepristone with Methotrexate in the Medical Management of Ectopic pregnancy

Name of the Investigator : **Dr. Niveditha**

Name of the Participant :

Name of the Institution : IOG, Egmore, Chennai-8.

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have informed the investigator of all the treatments I am taking or have taken in the past months/years including any native (alternative) treatments.
6. I have been advised about the risks associated with my participation in the study.*
7. I agree to cooperate with the investigator and I will inform him /her immediately if I suffer unusual symptoms. *
8. I have not participated in any research study within the past _____ month(s). *
9. I have not donated blood within the past _____ months. (Add if the study involves extensive blood sampling). *
10. I am aware of the fact that I can opt out of the study at any time without having to give any reasoned this will not affect my future treatment in this hospital. *
11. I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent. *
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC if required.
13. I understand that my identity will be kept confidential if my data are publicly presented.
14. I have had my questions answered to my satisfaction.
15. I consent voluntarily to participate in the research/study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

1. Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

   Name _____ Signature_____ Date_____

2. Name and Signature of impartial witness (required for illiterate patients):

   Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

3. Name and Signature of the investigator or his representative obtaining consent:

   Name _____ Signature_____ Date_____

Welcome to your new class homepage! From the class homepage you can see all your assignments for your class, view additional assignment information, submit your work, and access feedback for your papers.

Hover on any item in the class homepage for more information.

Class Homepage

This is your class homepage. To submit to an assignment click on the "Submit" button to the right of the assignment name. If the Submit button is grayed out, no submissions can be made to the assignment. If resubmissions are allowed the submit button will read "Resubmit" after you make your first submission to the assignment. To view the paper you have submitted, click the "View" button. Once the assignment's post date has passed, you will also be able to view the feedback left on your paper by clicking the "View" button.

Assignment Inbox: The Tamil Nadu Dr.M.G.R.Medical Uty 2014-15 Examinations

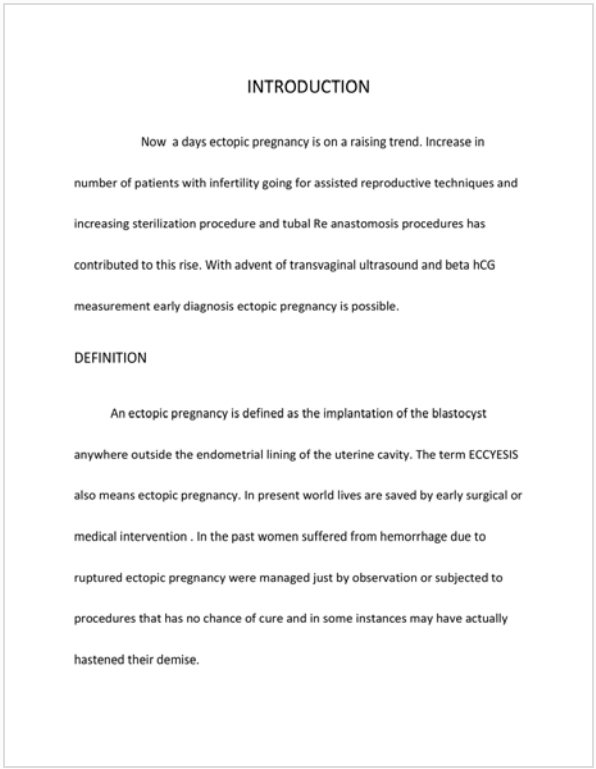
	Info	Dates	Similarity	
TNMGRMU EXAMINATIONS	ⓘ	Start 01-Sep-2014 11:27AM Due 30-Oct-2015 11:59PM Post 30-Oct-2015 12:00AM	22%	Resubmit View

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Chinnarajalu niveditha
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	COMPARATIVE STUDY OF MIFEPR..
File name:	FINAL_UPLOAD.doc
File size:	1.5M
Page count:	68
Word count:	5,280
Character count:	29,875
Submission date:	29-Sep-2015 01:16AM
Submission ID:	576821331



INTRODUCTION

Now a days ectopic pregnancy is on a raising trend. Increase in number of patients with infertility going for assisted reproductive techniques and increasing sterilization procedure and tubal Re anastomosis procedures has contributed to this rise. With advent of transvaginal ultrasound and beta hCG measurement early diagnosis ectopic pregnancy is possible.

DEFINITION

An ectopic pregnancy is defined as the implantation of the blastocyst anywhere outside the endometrial lining of the uterine cavity. The term ECCYESIS also means ectopic pregnancy. In present world lives are saved by early surgical or medical intervention . In the past women suffered from hemorrhage due to ruptured ectopic pregnancy were managed just by observation or subjected to procedures that has no chance of cure and in some instances may have actually hastened their demise.